EXHIBIT B

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

YENTREVE 40 mg hard gastro-resistant capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in YENTREVE is duloxetine.
Each capsule contains 40 mg of duloxetine as duloxetine hydrochloride.

Excipients: sucrose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

The capsule has an opaque orange body, imprinted with '40mg' and an opaque blue cap, imprinted with '9545'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

YENTREVE is indicated for women for the treatment of moderate to severe Stress Urinary Incontinence (SUI), (see section 5.1).

4.2 Posology and method of administration

The recommended dose of YENTREVE is 40 mg twice daily without regard to meals. After 2-4 weeks of treatment, patients should be re-assessed in order to evaluate the benefit and tolerability of the therapy. Some patients may benefit from starting treatment at a dose of 20 mg twice daily for two weeks before increasing to the recommended dose of 40 mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness.
However, limited data are available to support the efficacy of YENTREVE 20 mg twice daily.
A 20 mg capsule is also available.

The efficacy of YENTREVE has not been evaluated for longer than 3 months in placebo-controlled studies. The benefit of treatment should be re-assessed at regular intervals.

Combining YENTREVE with a pelvic floor muscle training (PFMT) program may be more effective than either treatment alone. It is recommended that consideration be given to concomitant PFMT.

Hepatic insufficiency:
YENTREVE should not be used in women with liver disease resulting in hepatic impairment (see section 4.3).

Renal insufficiency:
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min).

Elderly:
Caution should be exercised when treating the elderly.

Children and adolescents:
The safety and efficacy of duloxetine in patients in these age groups have not been studied. Therefore, administration of YENTREVE to children and adolescents is not recommended.

Discontinuation of treatment:
Abrupt discontinuation should be avoided. When stopping treatment with YENTREVE the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Liver disease resulting in hepatic impairment (see section 5.2).

Pregnancy and lactation (see section 4.6).

YENTREVE should not be used in combination with nonselective, irreversible Monoamine Oxidase Inhibitors - MAOIs (see section 4.5).

YENTREVE should not be used in combination with CYP1A2 inhibitors, like fluvoxamine, ciprofloxacin or enoxacine since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with YENTREVE is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Mania and Seizures
YENTREVE should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Use with antidepressants
The use of YENTREVE in combination with antidepressants (especially with SSRI, SNRI and reversible MAOIs) is not recommended (see below "Depression, suicidal ideation and behaviour" and Section 4.5).

Mydriasis
Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine in patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate
Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore,in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with drugs that may impair its metabolism (see section 4.5). For patients who experience a sustained

increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

Renal impairment
Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

Sucrose
YENTREVE hard gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Haemorrhage
There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

Discontinuation of treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a clinical trial adverse events seen on abrupt treatment discontinuation occurred in approximately 44% of patients treated with YENTREVE and 24% of patients taking placebo.
The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally the symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Hyponatremia
Hyponatremia has been reported rarely, predominantly in the elderly, when administering YENTREVE. Caution is required in patients at increased risk for hyponatremia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Depression, suicidal ideation and behaviour
Although YENTREVE is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. Isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on YENTREVE therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of YENTREVE is recommended (see Section 4.2).

Use in children and adolescents under 18 years of age
No clinical trials have been conducted with duloxetine in paediatric populations. YENTREVE should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Long-term safety

data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Medicinal products containing duloxetine
Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive episodes as well as stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

Hepatitis/increased liver enzymes
Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other drugs associated with hepatic injury.

Akathisia/psychomotor restlessness
The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): due to the risk of serotonin syndrome, YENTREVE should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping YENTREVE before starting an MAOI (see section 4.3).

Serotonin syndrome: in rare cases, serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. The use of YENTREVE in combination with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, venlafaxine, or triptans, tramadol and tryptophan is not recommended.

CNS drugs: caution is advised when YENTREVE is taken in combination with other centrally acting drugs or substances, including alcohol and sedative drugs (benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Effect of duloxetine on other drugs
Medicinal products metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily). *Medicinal products metabolised by CYP2D6:* Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if YENTREVE is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

Oral contraceptives and other steroidal agents: results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

Anticoagulants and antiplatelet agents: Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding.

Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin.

Effects of other drugs on duloxetine
Antacids and H2 antagonists: co-administration of YENTREVE with aluminium- and magnesium-containing antacids or with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

Inhibitors of CYP1A2: because CYP1A2 is involved in duloxetine metabolism, concomitant use of YENTREVE with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC_{0-t} 6-fold. Therefore YENTREVE should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

Inducers of CYP1A2: Population pharmacokinetic studies analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

4.6 Pregnancy and lactation

Pregnancy
There are no data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3). The potential risk for humans is unknown. Withdrawal symptoms may occur in the neonate after maternal duloxetine use near term. YENTREVE is contraindicated during pregnancy (see section 4.3).

Breast feeding
Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children . The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of YENTREVE while breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

Although in controlled studies duloxetine has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation and dizziness. Therefore, patients should be cautioned about their ability to drive a car or operate hazardous machinery.

4.8 Undesirable effects

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7977 patients, 4371 on duloxetine and 3606 on placebo) in SUI and other lower urinary tract disorders.
The most commonly reported adverse events in patients treated with YENTREVE in clinical trials in SUI and other lower urinary tract disorders were nausea, dry mouthand fatigue -. The data analysis of four 12-week, placebo-controlled clinical trials in patients with SUI, including 958 duloxetine-treated and 955 placebo-treated patients, showed that the onset of the reported adverse events typically occurred in the first week of therapy. However, the majority of the most frequent adverse events were mild to moderate and resolved within 30 days of occurrence (e.g. nausea).

Table 1: Adverse reactions
Frequency estimate: Very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥ 0.01% and <0.1%), very rare (<0.01%), frequency not known (data from spontaneous reports)

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
Infections and infestations					
		Laryngitis			
Immune system disorders					
		Hyper-sensitivity disorder			Anaphylactic reaction
Endocrine disorders					
		Hypo-thyroidism			
Metabolism and Nutrition Disorders					
	Appetite decreased	Dehydration			Hyponatremia, SIADH
Psychiatric Disorders					
	Insomnia Sleep disorder Anxiety Libido decreased Agitation	Bruxism Disorientation Orgasm abnormal Apathy Abnormal dreams			Hallucinations Mania
Nervous System Disorders					
	Headache Dizziness Tremor Nervousness Lethargy Somnolence Paraesthesia	Dysgeusia Disturbance in attention	Myoclonus Dyskinesia		Serotonin syndrome Extrapyramidal symptoms Convulsions Akathisia Psychomotor restlessness
Eye Disorders					
	Blurred vision	Mydriasis Visual disturbance	Glaucoma		
Ear and Labyrinth Disorders					
	Vertigo	Ear pain			
Cardiac Disorders					
	Palpitations	Tachycardia			Supra-ventricular arrhythmia, mainly atrial fibrillation
Vascular Disorders					
	Hot flush	Flushing Blood pressure increase Syncope[1]	Peripheral coldness Orthostatic hypotension[1] Hypertensive crisis		Hypertension
Respiratory, thoracic and mediastinal disorders					
		Yawning	Throat tightness		

Gastrointestinal Disorders					
Nausea (22%) Dry mouth (11.2%)	Constipation Diarrhoea Vomiting Dyspepsia	Eructation Gastroenteritis Stomatitis Halitosis Gastritis Flatulence			
Hepato-biliary disorders					
		Elevated liver enzymes (ALT, AST, alkaline phosphatase) Hepatitis[2] Acute liver injury			Jaundice Hepatic failure
Skin and Subcutaneous Tissue Disorders					
	Sweating increased	Night sweats Cold sweat Rash	Photo-sensitivity reactions		Angioneurotic oedema Stevens-Johnson Syndrome Urticaria
Muscoskeletal and connective tissue disorders					
		Muscle tightness Musculo-skeletal pain Trismus	Muscle twitching		
Renals and Urinary Disorders					
		Nocturia Urinary hesitation Urine odour abnormal Dysuria			Urinary retention
Reproductive System and Breast Disorders					
		Menopausal symptoms			
General Disorders and Administration Site Conditions					
Fatigue (10.3%)	Pruritus Weakness Abdominal pain Chills	Feeling hot Malaise Thirst Feeling abnormal	Feeling cold		Chest pain
Investigations					
		Weight increase Weight decrease Creatinine phosphokinase increase			

		Blood cholesterol increased			

[1]Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment
[2]See section 4.4

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions.
Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Electrocardiograms were obtained from 755 duloxetine-treated patients with SUI and 779 placebo-treated patients in 12-week clinical trials. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients.

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients . HbA_{1c} was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

4.9 Overdose

There is limited clinical experience with duloxetine overdose in humans. Cases of overdoses, alone or in combination with other drugs, with duloxetine doses of almost 2000 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed drugs) included serotonin syndrome, somnolence, vomiting and seizures.

No specific antidote for duloxetine is known but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered.. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21

Duloxetine is a combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

In animal studies, increased levels of 5-HT and NE in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle only during the storage phase of the micturition cycle. A similar mechanism in women is believed to result in stronger urethral closure during urine storage with physical stress that could explain the efficacy of duloxetine in the treatment of women with SUI.

The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four double-blind, placebo-controlled studies, that randomised 1913 women (22 to 83 years) with SUI; of these, 958 patients were randomised to duloxetine and 955 to placebo. The primary efficacy measures were Incontinence Episode Frequency (IEF) from diaries and an incontinence specific quality of life questionnaire score (I-QOL).

Incontinence Episode Frequency: in all four studies the duloxetine-treated group had a 50% or greater median decrease in IEF compared with 33% in the placebo-treated group. Differences were observed at each visit after 4 weeks (duloxetine 54%; and placebo 22%), 8 weeks (52% and 29%), and 12 weeks (52% and 33%) of medication.

In an additional study limited to patients with severe SUI, all responses with duloxetine were achieved within 2 weeks.

The efficacy of YENTREVE has not been evaluated for longer than 3 months in placebo-controlled studies. The clinical benefit of YENTREVE compared with placebo has not been demonstrated in women with mild SUI, defined in randomised trials as those with IEF < 14 per week. In these women, YENTREVE may provide no benefit beyond that afforded by more conservative behavioural interventions.

Quality of Life: Incontinence Quality of Life (I-QOL) questionnaire scores were significantly improved in the duloxetine-treated patient group compared with the placebo-treated group (9.2 versus 5.9 score improvement, $p<.001$). Using a global improvement scale (PGI), significantly more women using duloxetine considered their symptoms of stress incontinence to be improved with treatment compared with women using placebo (64.6% versus 50.1%, $p<.001$).

YENTREVE and Prior Continence Surgery: there are limited data that suggest that the benefits of YENTREVE are not diminished in women with stress urinary incontinence who have previously undergone continence surgery.

YENTREVE and Pelvic Floor Muscle Training (PFMT): during a 12-week blinded, randomised, controlled study, YENTREVE demonstrated greater reductions in IEF compared with either placebo treatment or with PFMT alone. Combined therapy (duloxetine + PFMT) showed greater improvement in both pad use and condition-specific quality of life measures than YENTREVE alone or PFMT alone.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Duloxetine is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%; N=8 subjects). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%).

Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both CYP2D6 and CYP1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy,6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

The elimination half-life of duloxetine after an oral dose ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr) After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Special populations:
Age: pharmacokinetic differences have been identified between younger and elderly females (≥65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose.

Renal impairment: end stage renal disease (ESRD) patients receiving dialysis had a 2-fold higher duloxetine C_{max} and AUC values compared to healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic insufficiency: moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Nursing mothers: The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown.

Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximun clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In pre/postnatal toxicity study in the rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposures levels below maximum clinical exposure (AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Hypromellose.
Hydroxypropyl methylcellulose acetate succinate
Sucrose
Sugar spheres
Talc
Titanium dioxide (E171)
Triethyl citrate.

Capsule Shell:
Gelatin
Sodium Lauryl Sulfate
Titanium Dioxide (E171)
Indigo Carmine (E132)
Red Iron oxide (E172)
Yellow Iron Oxide (E172)
Edible black ink.

Edible Ink:
Black Iron Oxide-Synthetic (E172)
Propylene glycol
Shellac

Capsule Shell Cap colour:
Opaque Blue

Capsule Shell Body colour:
Opaque Orange

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package. Do not store above 30°C.

6.5 Nature and contents of container

Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminum foil.

Packs of 28, 56, 98, 140 and 196 (2x98) capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/280/002
EU/1/04/280/003
EU/1/04/280/004
EU/1/04/280/005
EU/1/04/280/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 August 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

YENTREVE 20 mg hard gastro-resistant capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in YENTREVE is duloxetine.

Each capsule contains 20 mg of duloxetine as duloxetine hydrochloride.

Excipients: sucrose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

The capsule has an opaque blue body, imprinted with '20 mg' and an opaque blue cap, imprinted with '9544'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

YENTREVE is indicated for women for the treatment of moderate to severe Stress Urinary Incontinence (SUI), (see section 5.1).

4.2 Posology and method of administration

The recommended dose of YENTREVE is 40 mg twice daily without regard to meals. After 2-4 weeks of treatment, patients should be re-assessed in order to evaluate the benefit and tolerability of the therapy. Some patients may benefit from starting treatment at a dose of 20 mg twice daily for two weeks before increasing to the recommended dose of 40 mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness.
However, limited data are available to support the efficacy of YENTREVE 20 mg twice daily.

The efficacy of YENTREVE has not been evaluated for longer than 3 months in placebo-controlled studies. The benefit of treatment should be re-assessed at regular intervals.

Combining YENTREVE with a pelvic floor muscle training (PFMT) program may be more effective than either treatment alone. It is recommended that consideration be given to concomitant PFMT.

Hepatic insufficiency:
YENTREVE should not be used in women with liver disease resulting in hepatic impairment (see section 4.3).

Renal insufficiency:
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min).

Elderly:
Caution should be exercised when treating the elderly.

Children and adolescents:
The safety and efficacy of duloxetine in patients in these age groups have not been studied. Therefore, administration of YENTREVE to children and adolescents is not recommended.

Discontinuation of treatment:
Abrupt discontinuation should be avoided. When stopping treatment with YENTREVE the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Liver disease resulting in hepatic impairment (see section 5.2).

Pregnancy and lactation (see section 4.6).

YENTREVE should not be used in combination with nonselective, irreversible Monoamine Oxidase Inhibitors - MAOIs (see section 4.5).

YENTREVE should not be used in combination with CYP1A2 inhibitors, like fluvoxamine, ciprofloxacin or enoxacine since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with YENTREVE is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Mania and Seizures
YENTREVE should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Use with antidepressants
The use of YENTREVE in combination with antidepressants (especially with SSRI, SNRI and reversible MAOIs) is not recommended (see below "Depression, suicidal ideation and behaviour" and Section 4.5).

Mydriasis
Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine in patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate
Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore,in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used

with drugs that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

Renal impairment
Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

Sucrose
YENTREVE hard gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Haemorrhage
There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

Discontinuation of treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a clinical trial, adverse events seen on abrupt treatment discontinuation occurred in approximately 44% of patients treated with YENTREVE and 24% of patients taking placebo.
The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally the symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Hyponatremia
Hyponatremia has been reported rarely, predominantly in the elderly, when administering YENTREVE. Caution is required in patients at increased risk for hyponatremia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Depression, suicidal ideation and behaviour
Although YENTREVE is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. Isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on YENTREVE therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of YENTREVE is recommended (see Section 4.2).

Use in children and adolescents under 18 years of age
No clinical trials have been conducted with duloxetine in paediatric populations. YENTREVE should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children

and adolescents treated with antidepressants compared to those treated with placebo. Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Medicinal products containing duloxetine
Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive episodes as well as stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

Hepatitis/increased liver enzymes
Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other drugs associated with hepatic injury.

Akathisia/psychomotor restlessness
The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): due to the risk of serotonin syndrome, YENTREVE should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping YENTREVE before starting an MAOI (see section 4.3).

Serotonin syndrome: in rare cases, serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. The use of YENTREVE in combination with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, venlafaxine, or triptans, tramadol and tryptophan is not recommended.

CNS drugs: caution is advised when YENTREVE is taken in combination with other centrally acting drugs or substances, including alcohol and sedative drugs (benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Effect of duloxetine on other drugs
Medicinal products metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily). *Medicinal products metabolised by CYP2D6:* Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if YENTREVE is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

Oral contraceptives and other steroidal agents: results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

Anticoagulants and antiplatelet agents: Caution should be exercised when duloxetine is combined

with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin.

Effects of other drugs on duloxetine
Antacids and H2 antagonists: co-administration of YENTREVE with aluminium- and magnesium-containing antacids or with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

Inhibitors of CYP1A2: because CYP1A2 is involved in duloxetine metabolism, concomitant use of YENTREVE with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC_{0-1} 6-fold. Therefore YENTREVE should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

Inducers of CYP1A2: Population pharmacokinetic studies analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

4.6 Pregnancy and lactation

Pregnancy
There are no data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3). The potential risk for humans is unknown. Withdrawal symptoms may occur in the neonate after maternal duloxetine use near term. YENTREVE is contraindicated during pregnancy (see section 4.3).

Breast feeding
Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children . The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of YENTREVE while breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

Although in controlled studies duloxetine has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation and dizziness. Therefore, patients should be cautioned about their ability to drive a car or operate hazardous machinery.

4.8 Undesirable effects

Table I gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7977 patients, 4371 on duloxetine and 3606 on placebo) in SUI and other lower urinary tract disorders.
The most commonly reported adverse events in patients treated with YENTREVE in clinical trials in SUI and other lower urinary tract disorders were nausea, dry mouthand fatigue -. The data analysis of four 12-week, placebo-controlled clinical trials in patients with SUI, including 958 duloxetine-treated and 955 placebo-treated patients, showed that the onset of the reported adverse events typically occurred in the first week of therapy. However, the majority of the most frequent adverse events were mild to moderate and resolved within 30 days of occurrence (e.g. nausea).

Table 1: Adverse reactions
Frequency estimate: Very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥ 0.01% and <0.1%), very rare (<0.01%), frequency not known (data from spontaneous reports)

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
Infections and infestations					
		Laryngitis			
Immune system disorders					
		Hypersensitivity disorder			Anaphylactic reaction
Endocrine disorders					
		Hypothyroidism			
Metabolism and Nutrition Disorders					
	Appetite decreased	Dehydration			Hyponatremia, SIADH
Psychiatric Disorders					
	Insomnia Sleep disorder Anxiety Libido decreased Agitation	Bruxism Disorientation Orgasm abnormal Apathy Abnormal dreams			Hallucinations Mania
Nervous System Disorders					
	Headache Dizziness Tremor Nervousness Lethargy Somnolence Paraesthesia	Dysgeusia Disturbance in attention	Myoclonus Dyskinesia		Serotonin syndrome Extrapyramidal symptoms Convulsions Akathisia Psychomotor restlessness
Eye Disorders					
	Blurred vision	Mydriasis Visual disturbance	Glaucoma		
Ear and Labyrinth Disorders					
	Vertigo	Ear pain			
Cardiac Disorders					
	Palpitations	Tachycardia			Supraventricular arrhythmia, mainly atrial fibrillation
Vascular Disorders					
	Hot flush	Flushing Blood pressure increase Syncope[1]	Peripheral coldness Orthostatic hypotension[1] Hypertensive crisis		Hypertension
Respiratory, thoracic and mediastinal disorders					
		Yawning	Throat tightness		

Gastrointestinal Disorders					
Nausea (22%) Dry mouth (11.2%)	Constipation Diarrhoea Vomiting Dyspepsia	Eructation Gastroenteritis Stomatitis Halitosis Gastritis Flatulence			
Hepato-biliary disorders					
		Elevated liver enzymes (ALT, AST, alkaline phosphatase) Hepatitis[2] Acute liver injury			Jaundice Hepatic failure
Skin and Subcutaneous Tissue Disorders					
	Sweating increased	Night sweats Cold sweat Rash	Photo-sensitivity reactions		Angioneurotic oedema Stevens-Johnson Syndrome Urticaria
Muscoskeletal and connective tissue disorders					
		Muscle tightness Musculo-skeletal pain Trismus	Muscle twitching		
Renals and Urinary Disorders					
		Nocturia Urinary hesitation Urine odour abnormal Dysuria			Urinary retention
Reproductive System and Breast Disorders					
		Menopausal symptoms			
General Disorders and Administration Site Conditions					
Fatigue (10.3%)	Pruritus Weakness Abdominal pain Chills	Feeling hot Malaise Thirst Feeling abnormal	Feeling cold		Chest pain
Investigations					
		Weight increase Weight decrease Creatinine phosphokinase increase			

		Blood cholesterol increased			

[1]Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment
[2]See section 4.4

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions.
Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Electrocardiograms were obtained from 755 duloxetine-treated patients with SUI and 779 placebo-treated patients in 12-week clinical trials. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients.

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients . HbA_{1c} was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

4.9 Overdose

There is limited clinical experience with duloxetine overdose in humans. Cases of overdoses, alone or in combination with other drugs, with duloxetine doses of almost 2000 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed drugs) included serotonin syndrome, somnolence, vomiting and seizures.
No specific antidote for duloxetine is known but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered.. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21

Duloxetine is a combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

In animal studies, increased levels of 5-HT and NE in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle only during the

storage phase of the micturition cycle. A similar mechanism in women is believed to result in stronger urethral closure during urine storage with physical stress that could explain the efficacy of duloxetine in the treatment of women with SUI.

The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four double-blind, placebo-controlled studies, that randomised 1913 women (22 to 83 years) with SUI; of these, 958 patients were randomised to duloxetine and 955 to placebo. The primary efficacy measures were Incontinence Episode Frequency (IEF) from diaries and an incontinence specific quality of life questionnaire score (I-QOL).

Incontinence Episode Frequency: in all four studies the duloxetine-treated group had a 50% or greater median decrease in IEF compared with 33% in the placebo-treated group. Differences were observed at each visit after 4 weeks (duloxetine 54%; and placebo 22%), 8 weeks (52% and 29%), and 12 weeks (52% and 33%) of medication.

In an additional study limited to patients with severe SUI, all responses with duloxetine were achieved within 2 weeks.

The efficacy of YENTREVE has not been evaluated for longer than 3 months in placebo-controlled studies. The clinical benefit of YENTREVE compared with placebo has not been demonstrated in women with mild SUI, defined in randomised trials as those with IEF < 14 per week. In these women, YENTREVE may provide no benefit beyond that afforded by more conservative behavioural interventions.

Quality of Life: Incontinence Quality of Life (I-QOL) questionnaire scores were significantly improved in the duloxetine-treated patient group compared with the placebo-treated group (9.2 versus 5.9 score improvement, $p<.001$). Using a global improvement scale (PGI), significantly more women using duloxetine considered their symptoms of stress incontinence to be improved with treatment compared with women using placebo (64.6% versus 50.1%, $p<.001$).

YENTREVE and Prior Continence Surgery: there are limited data that suggest that the benefits of YENTREVE are not diminished in women with stress urinary incontinence who have previously undergone continence surgery.

YENTREVE and Pelvic Floor Muscle Training (PFMT): during a 12-week blinded, randomised, controlled study, YENTREVE demonstrated greater reductions in IEF compared with either placebo treatment or with PFMT alone. Combined therapy (duloxetine + PFMT) showed greater improvement in both pad use and condition-specific quality of life measures than YENTREVE alone or PFMT alone.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Duloxetine is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%; N=8 subjects). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%).

Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both CYP2D6 and CYP1A2 catalyse the formation of the two major metabolites glucuronide conjugate of

4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy,6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

The elimination half-life of duloxetine after an oral dose ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr) After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Special populations:
Age: pharmacokinetic differences have been identified between younger and elderly females (≥65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose.

Renal impairment: end stage renal disease (ESRD) patients receiving dialysis had a 2-fold higher duloxetine C_{max} and AUC values compared to healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic insufficiency: moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Nursing mothers: The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown.

Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximun clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In pre/postnatal toxicity study in the rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposures levels below maximum clinical exposure (AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Hypromellose.